IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	SEAN B. CARROLL, Ph.D. *et al.*		
Serial No.:	10/662,918	Group No.:	1644
Filed:	09/15/03	Examiner:	Kim, Y.
Entitled:	**CLOSTRIDIAL TOXIN DISEASE THERAPY**		

DECLARATION OF DR. DOUGLAS C. STAFFORD UNDER 37 C.F.R. § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

Date: May 24, 2007 By: Traci E. Light

TRACI E. LIGHT

Sir:

I, Douglas C. Stafford, under penalty of perjury, state that:

1. I was President and Chief Executive Officer of Ophidian Pharmaceuticals, Inc. at 5445 East Cheryl Parkway, Madison, WI 53711 ("Ophidian"). Ophidian was the original owner of the above-identified patent application.

2. I had supervisory responsibility for certain experimentation performed at Ophidian which has relevance to the subject matter in the above-referenced patent application. I have a Ph.D. degree in Immunology and was involved in the design and interpretation of studies described below.

3. During the 1990s, I supervised experiments where antibodies to Clostridium toxins were tested for the ability to protect against infection, i.e. these antibodies were administered prophylactically. Such an experiment can be found in an issued patent, U.S. Patent No. 5,762,934, a patent that shares some of the same lineage as the present case (both cases stem in part from U.S. Patent Application Ser. No. 07/985,321, filed Dec. 4, 1992). Example 9 (which is entitled In Vivo Protection Of Golden Syrian Hamsters From *C. difficile* Disease By Avian Antitoxins Against *C. difficile* Toxins A And B) shows that antibodies to a Clostridial toxin can be readily used prophylactically where (as with *C. perfringens*) the toxins are not automatically lethal. The basic experimental design was as follows:

> On day 1, each animal was orally administered 1.0 ml of one of the three antitoxin preparations (prepared in section (a) above) at the following timepoints: 0 hrs., 4 hrs., and 8 hrs. On day 2, the day 1 treatment was repeated. On day 3, at the 0 hr. timepoint, each animal was again administered antitoxin, as described above. At 1 hr., each animal was orally administered 3.0 mg of clindamycin-HCl (Sigma) in 1 ml of water. This treatment predisposed the animals to infection with *C. difficile.*

The results are described as follows:

> Treatment of hamsters with orally-administered toxin A and toxin B antitoxin (group CTAB) successfully protected 7 out of 7 (100%) of the animals from *C. difficile* disease. Treatment of hamsters with orally-administered toxin A antitoxin (group CTA) protected 5 out of 7 (71%) of these animals from *C. difficile* disease. Treatment using pre-immune IgY was not protective against *C. difficile* disease, as only 1 out of 7 (14%) of these animals survived.

Thus, Example 9 provides clear evidence that such an prophylactic approach works and, indeed, works well.

4. I have read U.S. Patent No. 4,748,018 cited by the Examiner. The 018 Patent teaches a method of passively immunizing a mammal against a condition caused by an antigen. However the invention requires the step of administering to the mammal immunizing amounts of an antibody obtained from a domesticated fowl which has been immunized against the antigen; the mammal being tolerant to the antibody by virtue of having a history of consumption of

antibody containing material derived from the egg of a fowl (emphasis added). If one followed the teaching of 018 there could be no medicament for human use since developing oral tolerance in humans is not commonly practiced, effective, or practical.

5. The Uemura, et al., paper cited merely provides extant knowledge that *Clostridium perfringens* responsible for food poisoning produce entertoxin. The paper further describes experiments to quantify the amount of SERUM antibody to type A toxin found in NORMAL persons. The paper offered no insight or suggestion on the existence, role in disease resistance, or medicament value of luminal toxin antibodies (or any antibodies for that matter) in *C. prefringens* disease. The authors could not even draw a clear line from antibody titers to the natural history of toxin mediated disease, specifically its possible role in disease prophylaxis. In fact the authors further confuse the issues by stating: [i]t is not possible at the present time to explain the high prevalence of enterotoxin antibody in human sera nor is the reason for the observed national difference known. Antibody production might be induced during acute *C. perfringens* food poisoning but could possibly also be due to prolonged absorption of enterotoxin in symptomless carriers who harbor high numbers of *C. perfringens* type A (page 471). According, the authors do not provide any information relevant to administration of an oral medicament.

Dated: MAY 22, 2007

By: _____
Douglas C. Stafford, Ph.D.